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# High-Dose Cytosine Arabinoside and L-Asparaginase in Refractory Acute Lymphoblastic Leukemia: The Children's Cancer Group Experience

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***Problem.*** Therapy of children with relapsed acute lymphoblastic leukemia (ALL) not achieving a second remission (CR2) after an initial reinduction attempt is problematic.

***Methods.*** 52 children with ALL in first relapse received high-dose cytosine arabinoside and L-asparaginase (HDAraC/L-Asp) after failed attempts to achieve CR2. AraC was given at a dose of 3 gm/m$^2$ q12 h × 4 on days 0–1 and 7–8. L-asparaginase was given IM 6,000 IU/m$^2$ 3 hours after the completion of each 2-day cycle of AraC.

***Results.*** Of the 42 surviving to day 28, 22 (42% of all patients) achieved CR2. Ten died before day 28 (19%); four from leukemia and six from infections or toxicity (12% regimen-related mortality). There were 17 bacterial infections (three fatal), 17 invasive fungal infections (12 fatal), one fatal adenoviral infection, and one non-fatal Pneumocystis pneumonia. One patient was surviving when lost to follow-up at four months and one patient survives over 5 years after transplant. Sixteen of the 22 patients who entered CR2 subsequently relapsed, five died of non-leukemic causes, and one was lost to follow-up. The median duration of second remission was 3 months (range 0.7 to 19 months).

***Conclusions.*** HDAraC/L-Asp rescue reinduction for relapsed childhood ALL achieves CR2 in ~40% of patients who fail reinduction, but remissions are short for most patients and maintenance of CR2 remains unsatisfactory. Med. Pediatr. Oncol. 30:233–239, 1998.


**Key words:** childhood ALL: first relapse; cytosine arabinoside; L-asparaginase

## INTRODUCTION

For children with newly-diagnosed acute lymphoblastic leukemia, over 95% will achieve a complete remission and about 70% will be cured [1–4]. However, about 30% of those children who achieve a first remission will relapse, most within 3 years of achieving first remission. A reinduction attempt will achieve a second remission in about 70% of these children [5–10]. If the primary reinduction attempt fails, subsequent attempts are often unsuccessful, due to resistant leukemia and/or chemotherapeutic toxicity. For those patients who achieve a second remission, aggressive maintenance therapy or bone marrow transplantation offers a small possibility for cure [5–21].

Between the years of 1980 and 1992, the Children's Cancer Group conducted three studies in children with ALL in first relapse. The first study, CCG-181P, utilized an induction regimen of vincristine, prednisone, and L-asparaginase (VPL) followed by cyclical courses of chemotherapy for three years or a marrow transplant for those with a matched sibling donor [22]. The second study (CCG-133F) was a feasibility study, reported elsewhere [23], studying a dose escalation of idarubicin combined with VPL (VPLI) for reinduction, whereas the third study (CCG-1884) was a randomized study comparing VPLI to a standard four-drug reinduction with vincristine, prednisone, L-asparaginase, and daunomycin (VPLD) [24].



In all three studies, patients who failed to achieve a remission with VPL, VPLD, or VPLI were eligible to receive a second reinduction attempt with high-dose cytosine arabinoside followed by L-asparaginase (HDAraC/L-Asp). This paper outlines the experience in the 52 children who received HDAraC/L-Asp as a second reinduction attempt on these three studies.

## METHODS

### Patient Eligibility

In all three studies, patients with relapsed ALL who were under the age of 21 years at original diagnosis were eligible for study entry if their relapse occurred while on initial therapy or within 12 months of having their initial therapy discontinued. Patients entered onto study between 4/1/80 and 4/8/92. Reinduction was attempted

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with either VPL, VPLD, or VPLI, according to protocol assignment. Vincristine, prednisone, and L-asparaginase were given in standard doses. On CCG-133F, the daunorubicin dose was 30 mg/m$^2$ on days 0, 7, and 14, but was 45 mg/m$^2$ on CCG-1884. The idarubicin dose was escalated from 10 to 15 mg/m$^2$ on days 0, 7, and 14 on CCG-133F, whereas the dose was set at 12.5 mg/m$^2$ then later amended to 10 mg/m$^2$ on CCG-1884. Patients with no response to the four-drug induction (over 30% blasts on day 14 or 28) or who had achieved only a partial remission (6–30% blasts) by day 28 were eligible to receive rescue reinduction with HDAraC/L-Asp. Informed consent was obtained in accordance with individual institutional policies approved by the Department of Health and Human Services.

### Treatment Protocol

Rescue reinduction consisted of AraC 3 gm/m$^2$ as a 3-hour infusion given every 12 hours for four consecutive doses on days 0 and 1, then repeated on days 7 and 8. L-asparaginase 6,000 IU/m$^2$ was given intramuscularly 3 hours following the fourth dose of AraC on days 1 and 8 (at hour 42). The second course (days 7–8) was given regardless of blood counts on day 7. A bone marrow examination was done on day 28 after the start of the rescue reinduction therapy. Patients achieving remission then proceeded to maintenance chemotherapy or marrow transplant at investigator option. Patients failing to achieve a remission on HDAraC/L-Asp were removed from protocol and treated per investigator option.

Maintenance chemotherapy varied with the protocol. In CCG-181P, patients received cycles of escalating intravenous methotrexate followed by L-asparaginase [25] alternating with vincristine/prednisone pulses and cycles of cyclocytidine. On CCG-133F and CCG-1884, maintenance consisted of vincristine/methotrexate/L-Asp [26] alternating with courses of HDAraC/L-Asp combined with either daunorubicin or idarubicin [23,24]. The preparative therapy for marrow transplant was not specified in the protocols, except for CCG-181P which utilized two regimens (cyclophosphamide with total body irradiation [TBI] or HDAraC with TBI) [22].

Patients receiving HDAraC/L-Asp rescue reinduction were followed for toxicity, relapse, event-free survival (EFS), and survival, regardless of their response to the rescue reinduction.

### Statistical Analysis

Remission success rate was calculated as the number of patients who were alive and in remission at the end of rescue reinduction divided by the number of patients entering this phase of the study. Patients who died during induction or who failed to achieve a remission marrow were considered induction failures. Survival and the durability of the remissions attained were expressed as survival and event-free survival (EFS) from the date of starting rescue reinduction, using the method of Kaplan and Meier [27]. An event was defined as failure to achieve second remission, death, or any subsequent relapse after achievement of second remission. Survival and EFS were analyzed for length of first remission ($<$18 months vs. $\geqslant$18 months), presence of chromosomal abnormalities, intensity of initial therapy, white blood count at diagnosis (50,000/mm$^3$ vs. higher), and response to reinduction therapy (CR vs. other) by the log rank statistic. Toxicities experienced during the induction course were scored utilizing the Children's Cancer Group standardized toxicity grading scale common to all CCG studies (copy available upon request).

## RESULTS

### Patient Population

A total of 289 eligible patients were entered onto the three studies (102 on CCG-181P, 90 on CCG-133F, and 97 on CCG-1884). The overall induction rate for VPL was 71% and was 62% and 64%, respectively, for VPLI and VPLD on CCG-133F and CCG-1884. A total of 52 patients received HDAraC/L-Asp reinduction (11 from CCG-181P, 26 from CCG-133F, and 15 from CCG-1884).

### Efficacy of Rescue Reinduction

Overall, 22 of the 52 patients (42%) achieved remission following HDAraC/L-Asp (55% on CCG-181P, 35% on CCG-133F, and 47% on CCG-1884). Of the 19 patients who were M2 at start of rescue reinduction, 12 (63%) achieved a second CR. Of the 33 patients who were M3 at start of rescue reinduction, 10 (30%) achieved a second CR ($P < 0.05$). There were 10 deaths (19%) during rescue reinduction; four patients died with progressive leukemia with or without concomitant infection or toxicity and six died primarily due to infection or toxicity without evidence of leukemia on biopsy or autopsy (12% regimen-related mortality). Of the 42 patients alive at day 28, 22 (52%) had a remission marrow (M1), two (5%) had an M2 marrow, and 18 (43%) had an M3 marrow. Table I outlines the outcomes of the reinduction and the causes of failure overall and on the three protocols.

### Survival and Event-Free Survival After Rescue Reinduction

Only one patient survives with adequate follow-up. This patient achieved a partial remission, with HDAraC/L-Asp, then received a matched sibling donor marrow transplant and now survives in continuous complete remission more than 5 years later. A second surviving patient was lost to follow-up only 4 months after achieving CR2.

The survival and EFS were 36% and 27% respectively

**TABLE I. Outcome of Rescue Reinduction***

| Protocol | Dates open | N | CR | NO CR | Ind Death | Infection |
|---|---|---|---|---|---|---|
| CCG-181P | 4/1/80–4/1/86 | 11 | 6 | 3 | 2 (0) | 4 (2) |
| CCG-133F | 10/13/86–4/15/88 | 26 | 9 | 13 | 4 (3) | 16 (1) |
| CCG-1884 | 5/15/90–4/8/92 | 15 | 7 | 4 | 4 (1) | 10 (2) |
| Total | 4/1/80–4/8/92 | 52 | 22 | 20 | 10 (4) | 30 (5) |

*Children with acute lymphoblastic leukemia were entered onto three consecutive trials. Patients who failed the primary reinduction attempt were then offered reinduction with high-dose cytosine arabinoside with L-asparaginase.
CR = complete remission at day 28 of reinduction. NO CR = alive without a remission marrow at day 28. Ind Death = death during reinduction before day 28 (death on or before day 28 from progressive disease as the primary cause). Infection = significant infectious complications during induction (deaths during induction with infection as the primary cause).

6 months from beginning the HDAraC/L-Asp. At 2 years, the survival and EFS were 4% and 2%. Sixteen of the 22 patients who achieved remission on HDAraC/L-Asp relapsed very soon after achieving remission (median 3 months, range 0.7–19 months). Two of these 16 patients relapsed after an initially successful marrow transplant. One patient died several months after receiving HDAraC/L-Asp while in continued remission; death was due to progressive fungal infection acquired during rescue reinduction. Three patients died of toxicity and two of infection shortly after marrow transplant.

A short first remission (<18 months), the presence of chromosomal abnormalities, the intensity of the initial therapy (standard VPL with VP pulses vs. other), and the white count at diagnosis (>50,000/mm$^3$) all failed to show any significant effect on survival or EFS, though for all four factors there was a trend toward both a worse survival and EFS in the presence of the adverse factor. The failure to achieve a second remission with rescue reinduction was significantly correlated with length of survival ($P = 0.04$).

### Toxicity of Rescue Reinduction

This rescue reinduction regimen utilizing HDAraC and L-Asp is highly toxic. The mean time to an absolute neutrophil count (ANC) of >500 neutrophils/mm$^3$ in those achieving a remission was 29 days. Almost all patients required platelet and red cell infusions. Half of the patients required total parenteral nutrition following the reinduction course. All patients required broad spectrum antibiotic therapy for fever with neutropenia. Over two-thirds received antifungal therapy for proven or suspected fungal infection. Fifteen patients developed documented bacterial sepsis (three fatal). Two patients developed an abscess without bacteremia; both survived. Seventeen patients developed evidence of systemic deep-seated fungal infections (12 fatal). One patient died of an adenoviral interstitial pneumonia and one survived Pneumocystis pneumonia. Table II summarizes the infectious complications seen during the rescue reinduction phase.

Other serious toxicities included one case of L-Asp associated diabetes mellitus and one moderately severe generalized exfoliative erythroderma attributed to HDAraC. Twenty percent of the patients developed grade 3 liver dysfunction.

## DISCUSSION

The majority of children with acute lymphoblastic leukemia are cured with aggressive chemotherapy currently in use [1–4]. Unfortunately, about 30% of children with ALL will suffer a relapse. About 70% or more of these children who relapse will achieve a second remission and up to 25% of these children may be cured with chemotherapy alone, more commonly, those patients who had initial remissions greater than 2–3 years [10,21]. Allogeneic transplant achieves a 25–60% relapse-free survival for those patients who have a suitable donor [5–21]. Those children who fail to achieve a second remission with the first reinduction attempt have an extremely poor chance for prolonged survival. This paper outlines the CCG experience in these very poor prognosis patients in whom we attempted to achieve second remission with a rescue reinduction consisting of high-dose cytosine arabinoside combined with L-asparaginase.

Among the 52 children treated in this manner over a 10-year period on three separate protocols, CR2 was attained in 42%. The children who failed to achieve CR2 either died during induction (12%) or had persistent leukemia. Among patients who achieved CR2 with HDAraC/L-Asp, second remissions were very short. Only two patients survive, one over 5 years after a marrow transplant and one who achieved an M1 marrow with reinduction but had a very short documented follow-up. Although the duration of remission in these patients was short, this rescue reinduction regimen may provide some patients the opportunity to undergo potentially curative therapy, such as allogeneic bone marrow transplantation.

Infections were a major complication of this intensive induction regimen. Overall, 28 of the 52 patients expe-

**TABLE II. Infectious Complications With Rescue Reinduction***

| Bacterial infection | | Invasive fungal infection | | Viral infection | | Protozoal infection | |
|---|---|---|---|---|---|---|---|
| Sepsis | | Candida | 7 (4) | Adenoviral | | *P carinii* Pneumonia | 1 (0) |
| *E. coli* | 3 (1) | Aspergillus | 4 (3) | Interstitial | | | |
| Klebsiella | 1 (0) | Fusarium | 1 (1) | Pneumonia | 1 (1) | | |
| Pseudomonas | 2 (1) | Fungus | 5 (4) | | | | |
| *S. aureus* | 2 (1) | (no identification) | | | | | |
| *S. epi* | 5 (0) | | | | | | |
| *S. mitis* | 1 (0) | | | | | | |
| Neisseria | 1 (0) | | | | | | |
| Malassezia furfur abscess | 1 (0) | | | | | | |
| Perirectal abscess (unknown organism) | 1 (0) | | | | | | |
| 17 bacterial infections (3 fatal) | | 17 fungal infections (12 fatal) | | 1 viral infection (1 fatal) | | 1 protozoal infection (0 fatal) | |

*Twenty-eight of the 52 patients experienced a total of 36 significant infectious complications during or as a direct consequence of rescue reinduction.
Number in parentheses represents deaths directly due to the infection listed.

rienced 36 serious life-threatening infections during rescue reinduction, 17 of which were fungal in origin. Perhaps prophylaxis with intravenous gammaglobulin [28] and antifungal agents such as fluconazole [29] as well as the use of cytokines such as GM-CSF or G-CSF [30] would diminish the acute risk of infection during or shortly after reinduction and thus improve the possibility of achieving CR2. Organ toxicity was tolerable, with only one death due to non-hematopoietic toxicity during the reinduction attempt, a gastrointestinal hemorrhage.

The Capizzi II HDAraC/L-Asp regimen and variations of this regimen have been used most commonly for AML, but some experience exists in the literature in patients with ALL. Welbron [31] reviewed the results with various reinduction regimens in relapsed adult ALL. Her review identified nine studies involving 87 patients in which HDAraC alone was utilized for reinduction of relapsed ALL. The CR rate ranged from 0 to 73%, with an overall remission induction rate of 34%. The regimen-related death rate was not reported in this group of patients. The median duration of remission overall was only 3.6 months. HDAraC was combined with an anthracycline and/or vincristine and a steroid in 15 studies involving 442 patients. The overall CR rate was 60%, but there was a 12% regimen-related mortality. The median duration of remission was only 3.4 months. HDAraC combined with L-Asp was reported in only two adult studies involving 16 ALL patients with a CR rate of 30%, similar to HDAraC alone. In a study by Wells et al. [32], 10 of 22 children with relapsed ALL achieved CR after HDAraC/L-Asp, but all relapsed at a median of 2 months after CR was achieved (range 1–5 months). Among the total of 41 patients treated (including 19 patients were AML), 21 developed infectious complications during induction, resulting in the death of five patients prior to day 28.

Some studies suggest that HDAraC regimens in relapsed ALL are associated with a lower incidence of CNS or extramedullary relapse than regimens not utilizing HDAraC and have been used successfully, specifically for treating patients with extramedullary relapse with or without marrow relapse [33–34].

## ACKNOWLEDGMENTS

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| Institution | Investigators | Grant No. |
|---|---|---|
| Children's Mercy Hospital<br>Kansas City, Missouri | Maxine Hetherington, M.D. | — |
| Univ. of Nebraska Medical Center<br>Omaha, Nebraska | Peter Coccia, M.D. | — |
| Cleveland Clinic Foundation<br>Cleveland, Ohio | Donald Norris, M.D. | — |
| Wyler Children's Hospital<br>Chicago, Illinois | F. Leonard Johnson, M.D. | — |
| M.D. Anderson Cancer Center<br>Houston, Texas | Beverly Raney, M.D. | — |
| Princess Margaret Hospital<br>Perth, Western Australia | David Baker, M.D. | — |
| Fred Hutchinson Cancer Research Center<br>Seattle, Washington | Jean Sanders, M.D. | — |
| New York Univ. Medical Center<br>New York, New York | Aaron Rausen, M.D. | — |
| Children's Hosp. of Orange County<br>Orange, California | Mitchell Cairo, M.D. | — |